partial response was demonstrated after 6 cycles of OGT 719 at 250 mg/m^2 on days 1 to 5 (renal cell carcinoma with liver metastases). Two patients had stable disease after 6 cycles of OGT 719 at 1000 mg/m^2 on days 1, 3 and 5 (metastatic adenocarcinoma) and 1750 mg/m^2 on days 1 to 5 (melanoma with lung metastases). Pharmacokinetic data show no accumulation with daily dosing and dose linearity for AUC and Cmax up to 10000 mg/m^2 is apparent.

Conclusions: These data indicate that OGT 719 has predictable pharmacokinetics with more variability at the higher doses. Structural modification of 5-FU with a carbohydrate ligand significantly affects potency on a mg/m^2 basis.

1155 POSTER

Phase I and pharmacokinetic study of BBR 2778

S. Faivre[1], E. Raymond[1], M. Gatineau[1], X. Buthaut[1], V. Boige[1], S. Mekhaldi[1], P. Pautier[1], M. Ducreux[1], G. Camboni[2], J.P. Armand[1]. [1]*G. Roussy, Médecine, Villejuif, France;* [2]*Boehringer Mannheim, Roche, Monza, Italy*

BBR 2778, a novel anthracenedione, induces DNA intercalation and inhibition of the topoisomerase-II enzyme. In this study BBR 2778 was given as a 1 h intravenous infusion weekly for 3 weeks (w) every 4 w. The aims were (1) to study the pharmacokinetics (PKs), (2) to determine the maximum tolerated dose (MTD), (3) to define dose-limiting toxicities (DLT), and (4) to recommend a dose for phase II studies. Dose escalation proceed according to the following weekly dose-levels (mg/m^2): 5 (4 pts, 9 cycles), 10 (3 pts, 3 cycles), 16.5 (3 pts, 5 cycles) 25 (6 pts, 9 cycles), 37.5 (1 pt, 1 cycle), 75 (4 pts, 5 cycles), 112.5 (6 pts, 10 cycles), 150 (3 pts, 4 cycles). Plasma PKs followed a multiexponential profile with a rapid distribution phase followed by a prolonged elimination phase. BBR 2778 had a large volume of distribution and was efficiently cleared from the plasma compartment. DLT was neutropenia. Other toxicities were mild to moderate including lymphopenia, thrombocytopenia, alopecia, and moderate nausea/vomiting. No cardiac toxicity was reported. The MTD was 150 mg/m^2/w for 3w, q4w (2/3 DLT) and the recommended dose for phase II studies was 112.5 mg/m^2/w for 3w, q4w.

1156 POSTER

Biweekly docetaxel (DOC), gemcitabine (GEM), oxaliplatin (LOHP) in heavily pretreated patients with solid tumors – Preliminary results of a phase I study

T. Büchele[1], A. Grothey[1], W. Voigt[1], T. Kegel[1], C. Rie[1], D. Wunderlich[1], H.J. Schmoll[1]. [1]*Martin-Luther-University Halle, Hematology/Oncology, Halle, Germany*

Purpose: In vitro data suggests a schedule-dependend synergistic antineoplastic activity of Doc/Gem/LOHP. To evaluate the toxicity of this novel triple combination, a pilot trial with 10 pts with refractory tumors was conducted with a biweekly application of this combination. Protocol (dose-level 0): Doc 35 mg/m^2 1 hr-infusion d1 (with standard premedication), followed after 1 hr rest by Gem 800 mg/m^2 30 min-infusion, followed by LOHP 65 mg/m^2 2 hrs infusion on d2; q d15 until progression. Based on the results of this 10 pts, a dose-escalation study was initiated. At time of this interim analysis 17 pts are evaluable for toxicity, 13 for response.

Patient characteristics: 12 male/5 female, median age 58 yrs, median ECOG-Status 1, median prior chemotherapies 2. Type of treated tumors: Squamous cell carcinoma of head and neck (10 pts), sarcoma (2 pts), CUP, gastric cancer, adrenal-, nasopharyngeal- and ovarial-carcinoma 1 pt.

Results: Toxicity (CTC-NCI-criteria): To date, 90 cycles are evaluable, median 5 cycles/pt (range: 3–10). Diarrhea II°: 1 pt, mucositis II° 1 pt, nausea/vomiting I/II° 4 pts, neurotoxicity I° 3 pt, IV° 1 pt (this patient has received 10 applications), no hematologic toxicity >2°; alopecia II° 5 pts, no other toxicity occurred.

Response: 3 (23%) objective remissions (sarcoma, head and neck, CUP) were seen. 8 pts (62%) showed disease stabilisation, 4 of them with clinical benefit (decrease of clinical symptoms or tumor markers). 2 pts (15%) progressed under therapy.

Conclusion: The application of Doc/Gem/LOHP is feasible in an outpatient setting and shows promising activity. One pt was taken of study due to neurotoxicity IV° after 10 applications. The patient cohort of this dose level was escalated to 6 pts. No further neurotoxity >II° occurred in this cohort in pts with a nearly similar number of applications. Dose-escalation continues further. Updated results of the dose-escalation study will be presented at the meeting in September 1999.

1157 POSTER

Escalated dose docetaxel (TXT) with G-CSF support in patients (PTS) with solid tumours

P. Mitchell[1], R. Basser[3], S. Ng[2], P. Gibbs[1], M. Chipman[1], A. Grigg[2], J. Gargano[4], A. Riva[4], F. Appia[4], M. Green[2]. [1]*Austin & Repatriation Medical Centre, Oncology, Melbourne;* [2]*Royal Melbourne Hospital, Oncology, Melbourne;* [3]*Western Hospital, Oncology, Melbourne;* [4]*Rhone-Poulenc Rorer, Research & Development, Melbourne, Australia/Paris, France*

Patients received TXT with G-CSF (lenograstim) support in a phase I dose escalation study, aiming to reduce dose limiting toxicities (DLTs) of neutropenia and sepsis. A 3 day steroid prophylaxis was given and pts received G-CSF 5 (ug/kg/d sc) from day 2 until neutrophils >1 × 10 9/l. 35 pts with various solid tumours were entered. Median age was 59 yrs (29–76) and 16 pts had previously received chemotherapy. TXT dosing was escalated by 10 mg/m^2 for cohorts of 3–6 pts, commencing at 110 mg/m^2 q21 days. At TXT170 mg/m^2, 2/3 pts experienced DLTs: grade III neuropathy and grade III skin toxicity respectively. Only two pts had DLTs at lower dose levels (130 mg/m^2). Twelve pts have now been treated at the recommended dose of 160 mg/m^2 without DLTs. The median neutrophil nadir occurred prior to day 8 with day 8 being the median day of cessation of lenograstim. Grade IV neutropenia was observed in 10/29 pts (35%). Only 3 pts developed febrile neutropenia which was not prolonged. Mobilisation of progenitor cells has been examined during cycle one for patients at all dose levels. Median CD34+ cell levels rose to 2.2 × 10 6/l on day 8 and 60% of pts had peak levels >1 × 10 6/l. A Phase II trial of TXT 160 mg/m^2 and lenograstim is currently being undertaken of pts with breast cancer who have not previously received chemotherapy for advanced disease.

1158 POSTER

A dose finding and pharmacokinetic study of docetaxel (TXT) and methotrexate (MTX) in patients with epithelial cancer

S. Zanetta[1], A. Guillot[1], C. Ardiet[1], B. Tranchand[1], A. Dumortier[1], E. Bernard[1], M. Peguy[1], S. Assadourian[2], J.P. Droz[1]. [1]*Centre Léon Berard, Lyon;* [2]*Laboratoires Rhône-Poulenc Rorer, Montrouge, France*

TXT and MTX, very active drugs in epithelial cancer, were associated and evaluated in a phase I study. TXT was given on day 8 as 1 hour infusion with dose escalation and MTX on d1 and 8 at fixed dose (40 mg/m^2). DLT was defined as NCI-CTC >2 toxicity, vomiting, diarrhea and stomatitis gr. >3 or a prolonged (>7 d) or febrile gr. 4 neutropenia (FN). 28 pts have been treated. Pts characteristics are: median age 55 [44–71], 5 females/23 males, PS 0:8 pts, 1:15 pts, 2:5 pts, tumor type: urothelial: 12, head and neck: 12, lung: 3, cervix: 1. All 28 patients are evaluable for toxicity. PK data were analyzed using NONEM, according to a 3 compartment model for both drugs. Co-variables were mainly age, body weight and surface area, sex, renal and hepatic parameters, α 1-acid glycoprotein. Major DLTs on cycle 1 were: FN (4), thrombocytopenia (3), cytolysis (3), stomatitis (2). Combination of TXT and MTX is feasible without severe toxicity and has notable activity. Adjunction of cisplatinum will be evaluated in a new phase I study

Dose Level		Toxicities (Nb of pts)		Obj.	PK Data (mg l^{-1}·h)	
TXT mg/m^2	MTX mg/m^2	Entered/ Evaluable	with cy 1 DLT	Resp.	AUC TXT 16 pts/28	AUC MTX 19 pts/28
60	40	3/3	0	1/3	2.32 ± 0.34	7.54 ± 1.71
70	40	6/6	0	1/6	3.48 ± 1.19	7.59 ± 1.63
80	40	7/6	2	2/7	4.27 ± 1.47	7.37 ± 1.97
90	40	6/6	3	1/6	4.59 ± 1.07	7.97 ± 1.44
100	40	6/6	2	–	–	–

1159 POSTER

Phase I trial and pharmacokinetic (PK) study of S16020 according to a weekly and every 2 week (W) schedule in cancer patients (PT)

E. Brian, M. Di Palma, A. Etassami, R. Quabdesselam, B. Gérard, N. Chouaki, C. Lucas, M.H. Brillanceau, B. Giroux, F. Turpin, J.L. Misset. *Centre René Huguenin St Cloud 92, Hôopital P. Brousse Villejuif 94, CAC Kremlin Bicêtre 94, I.R.I. Servier Courbevoie 92, France*

In a previous phase I study carried out with the new Olivacine derivative S16020 according to a single dose schedule (1 or 3 hour infusion) every

3 w, cutaneous side effects (hidradenitis and microkystic acnea) were the main dose limiting toxicity (DLT). In order to improve the therapeutic index, a weekly schedule D1, D8 and D15 of monthly cycles (one w rest) was initiated using an escalating dose scheme starting at 35 mg/m^2/w (4 pts level I), then 45 (5 pts level II) and 55 mg/m^2/w (3 pts level III). 12 pts were included having received from I up to 18 ad. (total 72 median 4). Main side effects were asthenia (WHO Grade 3 in 1 pt level III) and mild skin erythema (Grade 1–2 in 5 pts level II and III) and microkystic acnea (grade 1 in 1 pt level III). Nausea, vomiting and headache were prevented with setron and paracetamol premedications. MTD was not achieved but blood PK analysis showed evidence of a non linear kinetics with time between D1, D8 and D15 as shown by a 2 fold increase in clearance. Higher blood levels of the N-oxyde metabolite were found on D8 and D15 in comparison to D1. Clearance returned to base line values on D29 suggesting that a 2 week interval might be sufficient to achieve a reproducible exposure to S16020. Although the weekly schedule was well tolerated, the variability and the uncontrolled exposure to S16020 was not compatible with a development in phase II. Thus the protocol has been amended with a 2 week schedule and kinetic investigations. 5 pts have been included so far (3 at 55 and 2 at 65 mg/m^2 dose level). 2 pts developped an erythematous rash grade 2. MTD is not yet reached. Preliminary PK indicated a stable clearance over a 2 month period of treatment. A stable disease was documented in 1 pt with advanced renal carcinoma having received 18 ad. in the weekly schedule. Final results and PK analysis will be presented.

1160 POSTER

Oxaliplatin (L-OHP) + Tomudex (TOM) and levo-folinic acid (LFA) + 5-fluorouracil (5FU) every 2 weeks. A dose finding study in advanced colorectal carcinoma (ACC)

R. Casaretti[1], L. De Lucia[2], F. De Vita[3], A. Avallone[1], M. Orditura[3], A. Gravina[1], R. D'Aniello[1], P. Comella[1], G. Catalano[3], G. Comella[1]. [1]*Med. Oncol. A of Natl Tumor Inst. of Naples;* [2]*AORN of Caserta;* [3]*2nd Univ. Medical School of Naples, Italy*

Purpose: To define the MTD of L-OHP + TOM followed by LFA + 5FU, given q 2 wks in ACC patients.

Methods: L-OHP 85 mg/sqm (2 h i.v. infusion) → TOM 2.5 mg/sqm (15 min i.v. infusion) were given on d 1, LFA 250 mg/sqm (2 h i.v. infusion) → 5FU 750 mg/sqm (i.v.) were given on d 2. Courses were repeated every 2 wks. TOM and 5FU were alternately escalated if ≤4/6 patients showed the same DLT at the previous dose level. Then L-OHP will be escalated up to 130 mg/sqm. 27 pts with ACC were enrolled: 18 pretreated with 1, and 7 with 2 lines of CT. Liver/lung mets in 16/9 pts. 1/2/3 sites of disease in 9/10/8 pts.

Results: 5 dose levels have been tested so far without encountering the MTD.

L-OHP/TOM/5FU	No. pts	DLT Type	No. Cy.	N*	D*	S*	Neu*	
85/2.5/750	5	0/5		31	2	1	0	2
85/2.5/*900*	6	1/6	N4	35	2	0	0	0
85/*3.0*/900	7	3/6	N4, D3, S4	20	4	1	1	0
85/3.0/*1050*	6	0/6		20	0	0	0	0
105/3.0/1050	3	1/3	N4	7	1	0	0	0

*WHO g 3–4 neutropenia (N), diarrhea (D), stomatitis (S), neurotoxicity (Neu)

2/18 (11%) evaluable pts obtained a PR, while 13 pts showed MR (1) or SD (12).

Conclusions: Full doses of all cytotoxic drugs can be safely administered q 2 wks. G3–4 N is the main toxicity of this combination.

1161 POSTER

Phase I study of men-10755 in patients with a solid tumor as a short i.v. infusion given once every 3 weeks

M. Roelvink[2], S. Aamdal[1], P. Dombernowsky[1], J. Wanders[2], S. Peters[2], S. Bortini[3], A. Crea[3], A. Animati[3], A.-R. Hanauske[1]. [1]*EORTC-Early Clinical Studies Group, Brussels, Belgium;* [2]*Free University Hospital, New Drug Development Office, Amsterdam, Netherlands;* [3]*Menarini Research S.p.A., Clinical Research & Development, Florence, Italy*

Introduction: MEN-10755(M) is a third generation anthracycline showing better antitumor efficacy in preclinical models than doxorubicin.

A Phase I trial is currently ongoing in Denmark and Norway, investigating the feasibility of a tri-weekly schedule administering M as a short i.v. infusion. Main inclusion criteria are normal organ functions, no prior anthracyclines and LVEF >50%.

Results: Presently, thirty pts with a variety of tumor types have been enrolled, 19 M/11 F, median age 53 (range 31–69), median PS 1 (range 0–2). Twenty-one pts had no prior chemotherapy. Doses range from 4 to 110 mg/m^2. Pts were treated for a mean number of 3.8 cycles. Dose-limiting neutropenia was seen in 4 pts at dose levels 55, 80 and 110 mg/m^2 (1/6, 1/6 and 2/5, respectively). Major other grade 3–4 side-effects were nausea (13 pts) and vomiting (12 pts) without prophylactic antiemetics during the first cycle, but well controlled with oral antiemetics in consecutive cycles.

A reduction in LVEF, not correlated to cumulative dose and not accompanied by clinical symptoms was seen in 4 patients (65–49%, 72–57%, 77–60%, 70–55%). The last pt with LVEF reduction recovered after 5 weeks to baseline values. The other pts were not followed up.

No PR or CR was seen and five pts had stable disease as their best response.

M was assayed in plasma and urine using a validated HPLC method. Plasma and urine pharmacokinetics data (mean ± sd) were: CL = 6.3 ± 2.5 L/h/m^2, half-life = 19.1 ± 5.1 h, Vss = 87.6 ± 38.3 L/m^2, amount excreted unchanged in the urine = 10.2 ± 4.2% of the dose. In the range of the doses tested the kinetic of the drug is linear.

Conclusion: The maximum tolerated dose (MTD) was determined at 110 mg/m^2. A lower dose level of 100 mg/m^2 is currently under investigation.

Phase II trials will be conducted in sarcoma, non small cell lung cancer, small cell lung cancer, breast, ovarian, gastric and prostate cancer.

1162 POSTER

A Phase I study of 'Tomudex' and gemcitabine in advanced cancer

C. Cripps[1], G. Batist[2], S. Dahrouge[1], D. Fry[1], A. McQuillan[2], R. Kolendowicz[3], A.A. Abugaber[3]. [1]*Ottawa Regional Cancer Centre, Ontario;* [2]*Clinical Research Unit, Jewish General Hospital; Quebec;* [3]*Zeneca Pharmaceuticals, Canada*

Objectives: 'Tomudex' (raltitrexed) and gemcitabine are novel chemotherapeutic agents with a broad spectrum of activity and different mechanisms of action. We undertook a Phase I dose-escalation study of 'Tomudex' and gemcitabine to determine the DLT, MTD and RD for Phase II trials.

Methods: Eligibility criteria included: incurable solid cancer; [less than/= 1] prior treatment for metastatic disease; age >/= 18 yrs; ECOG performance status 0–2. Doses in cohort 1 were 'Tomudex' 2.0 mg/m[2] (15-min infusion) on day 1 followed by gemcitabine 800 mg/m[2] (30-min infusion) on days 1 and 8, q3 wks. Doses were escalated in 0.5 mg/m[2] increments for 'Tomudex' in cohorts 2, 3, and 4 and as a single increment of 200 mg/m[2] for gemcitabine in cohort 5. At least 3 pts were entered per cohort plus 3 further pts if 1/3 pts experienced a DLT. Further pts were entered at the RD to confirm tolerability.

Results: 30 pts have been treated (20 M/10 F: cohort 1, 3 pts; 2, 9 pts; 3, 5 pts; 4, 10 pts; 5, 3 pts). Primary diagnoses were: colorectal (8 pts), kidney (4 pts), stomach (3 pts), esophagus, pancreas, sarcoma, and small bowel (2 pts each), and breast, head and neck, melanoma and NSCLC (1 pt each), and unknown (3 pts). DLTs were experienced by 2/9 pts in cohort 2 (both grade III thrombocytopenia), 1/5 pts in cohort 3 (diarrhea and rash, both grade III), and 2/3 pts in cohort 5 (grade III shortness of breath, probably gemcitabine-related pneumonitis, and grade III thrombocytopenia). 1/8 evaluable pts in cohort 4 (1 further pt to be entered) experienced a DLT (diarrhea and rash, both grade III). 2/19 pts evaluable for efficacy had a PR (small bowel and colon; 1 unconfirmed), and 12 SD.

Conclusions: The likely RD is 'Tomudex' 3.5 mg/m[2] on day 1 and gemcitabine 800 mg/m[2] on days 1 and 8. This combination schedule is well tolerated and appears to have efficacy. Phase II studies of this combination will start shortly in pts with pancreatic and breast cancer.

Supported by a grant from Zeneca Pharma Inc.

'Tomudex' is a trade mark, the property of Zeneca Ltd.

1163 POSTER

A dose finding and toxicity study of the gemcitabine-oxaliplatin combination in patients with advanced solid tumors

D. Mavroudis, S. Agelaki, K. Kalbakis, Ch. Kouroussis, S. Kakolyris, N. Androulakis, J. Souglakos, N. Vardakis, G. Samonis, V. Georgoulias. *University, General Hospital of Heraklion, Dpt of Medical Oncology, Heraklion, Crete, Greece*

Background: Preclinical studies have shown synergistic activity for platinum compounds in combination with gemcitabine (GMB). Oxaliplatin (L-OHP) is a new platinum analog with better toxicity profile and partial